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Irritable Bowel Syndrome – New Drugs in the pipeline

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ABSTRACT
The term inflammatory bowel disease includes a group of disorders where the intestines become inflamed as a result of an auto immune reaction. The goal of medical treatment here is to suppress such abnormal inflammatory responses which can allow the intestinal tissue to heal, thereby relieving the symptoms of diarrhea and abdominal pain associated with inflammatory bowel diseases. A stepwise approach of the use of medications for inflammatory bowel disease includes aminosalicylates, corticosteroids, immune modifiers, anti-TNFagents, and antibiotics. Surgical treatment in such affected persons also varies, depending upon the stage of the disease. On the contrary, excessive surgical intervention can lead to more harm than benefit. So there is always a search for new drugs for better efficacy and potency.

KEY WORDS: clinical trials, inflammation, IBS, novel drugs , neurotransmitters

INTRODUCTION

Irritable bowel syndrome or IBS is a chronic functional disorder that is found in high prevalence throughout the world. Affected patients experience recurrent episodes of abdominal pain or discomfort associated with a change in the normal bowel pattern, such as diarrhoea and or constipation. It is estimated that IBS affects up to 15% of the population with its symptoms of chronic abdominal pain and major disturbances of bowel functioning. IBS can entail bouts of urgent diarrhoea, episodes of chronic constipation, or a pattern of alternating between the two Thus there are basically three forms of IBS depending on the symptoms — diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) and IBS with alternating diarrhoea and constipation (A-IBS) [1].

While the exact etiology and pathophysiology of IBS is unknown, it may be due to a disturbance in the interaction between the intestines, the CNS and the ANS that alters the regulation of bowel motility and its sensory functions. Noradrenaline and serotonin are the neurotransmitters that are known to be involved in the control of the gastrointestinal system. Apart from noradrenaline, the 5-HT_3 receptor also modulates the visceral sensitivity via the extrinsic sensory neurons and thus causes increased gastric emptying, whereas the 5-HT_4receptor modulates the peristaltic reflex and visceral sensitivity via the intrinsic sensory neurons [2]. So the unique combination of noradrenaline reuptake inhibition and 5-HT_3 antagonism in one orally delivered compound may represents a novel approach in treating IBS-D and other functional GI diseases. However the existing treatment for diarrhea-predominant IBS (IBS-D) includes antidiarrheals (eg, loperamide), antidepressants (eg, tricyclic antidepressants), antispasmodics (eg, dicyclomine), and the 5-HT_3 receptor antagonists [3].

Recent approaches to the pathophysiology of IBS have changed from spastic colitis to mucosal immune activation and inflammation which is supported by animal studies [4]. Generally, in 7%-30% of patients, there is a history of recent bacterial gastroenteritis, and inflammatory reaction to the infection which may increase the levels of cytokines and other inflammatory cells [5]. There is hence an imbalance between the pro-inflammatory and anti-inflammatory cytokines in patient of IBS.

NEW DRUGS FOR IBS IN CLINICAL TRIALS

Despite the wide range of medications and a high prevalence of the disease, till date no completely effective remedy is still available. Although various classes of drugs are being used in therapy, there are still the hopes for new drug investigations. The present review brings into light certain novel drugs either in clinical trials or in pipeline.

RENZAPRIDE

Renzapride, like cisapride & mosapride, is a substituted benzamide compound which has full agonist actions at 5-HT_4 receptor, partial agonist actions at 5-HT_3 and antagonist actions at 5-HT_{2b} receptor, thereby has prokinetic & antiemetic properties. It is currently in the Phase III clinical trials in the United States for the treatment of constipation-predominant irritable bowel syndrome (IBS-C). Various studies suggests efficacy of the drug in both men and women, but the beneficial action is predominant in women [6]. Evidence based studies suggests that both cisapride and renzapride enhance the contractions of an electrically stimulated ileum, but not the contractions caused by exogenous ACh thereby suggesting their actions to be due to stimulation of cholinergic neurons .

CILANSETRON

A novel 1,7-annelated indole, a selective antagonist for the serotonin type-3 (5-HT_3) receptor is currently under the phase III clinical trials.5HT_3 receptors in the G.I tract are responsible for causing nausea and increased gastrointestinal motility . In IBS, these receptors have become either faulty or hypersensitive. 5HT_3 antagonists thus work by blocking these

receptors. Results from two large, randomised, double-blind, placebo-controlled, parallel-group Phase III clinical trials of cilansetron in patients with IBS-D have shown that cilansetron was more effective than placebo at improving overall, as well as individual symptoms, including abdominal pain and diarrhoea both in female and male patients[7, 8].The most commonly reported side effect with cilansetron was constipation but in general, the drug was well tolerated .

It was seen that Cilansetron is well tolerated in patients. The most commonly reported adverse effects in clinical trials included constipation (8%-19%), abdominal pain (5%-8%), headache (6%-11%), increased creatinine phosphokinase (CPK) (2% in the 6-month study and 10% in the 3-month study) and nasopharyngitis (2%). Although rare, the most concerning side effect observed with cilansetron was ischaemic colitis, the event rate of which was 3.77 per 1000 person years of exposure [9]. Proposed mechanisms for this adverse effect with cilansetron, is due to an exaggerated vasoconstrictor response in elderly patients with diabetes , atherosclerosis or lipid dysfunction. Adverse effects were neither duration nor dose-dependent. Rates of constipation with cilansetron in clinical trials were 8%-19% .But by and large, cilansetron was extremely well tolerated and highly efficacious.

ASIMADOLINE

An orally administered drug that acts as a kappa (opioid) receptor agonist, *is in phase II trials*. Kappa receptors are found mostly in the G.I tract and play an important role in the control of visceral pain and bowel motility. Hence kappa agonists can relieve the pain, discomfort and impaired motility common to IBS and other gastrointestinal disorders. Asimadoline has approximately 500-fold greater selectivity for human kappa receptors as compared to either delta or mu, opioid receptors[10].Furthermore, asimadoline has selective peripheral actions at doses below 5 mg[11].In animal models of visceral pain, kappa-opioid agonists act to reduce visceral nociceptive reflex behaviour associated with colorectal distension [12].In a barostat model with IBS patients, asimadoline significantly reduced the area under the pressure-pain curve as compared to placebo, suggesting its visceral antinociceptive properties. Thus in a prospectively defined, clinically relevant patient subgroup, asimadoline shows efficacy in the treatment of D-IBS.

NEPADUTANT

Nepadutant is a potent and selective antagonist of tachykinin NK_2 receptors currently in phase II clinical trials. Tachykinins (TKs) are a family of neuropeptides, widely distributed in the gastrointestinal tract, where they function as excitatory neurotransmitters by binding to NK_1, NK_2 and NK_3 receptors. NK_2 receptors activation regulates intestinal motility and can cause both prokinetic and inhibitory effects, of which the latter is more evidenced in inflammatory conditions of the intestine [13]. NK_2 receptor antagonists can also affect the processes of water absorption/secretion across the intestinal wall. antiinflammatory effects associated with a reduction of tissue injury. Thus tachykinin NK_2 receptor antagonists can reduce motility and symptoms in gastrointestinal diseases characterized by local inflammation such as diarrhea or colitis.

Animal studies have shown that nepadutant produced a dose-dependent inhibition of the transit time of the small intestine as measured by the charcoal test in 7-15 days old newborn rats. It also reduced the abdominal contractions that were increased after colonic application of acetic acid in 14-15 days old newborns rats at doses of 0.5 and 2.5 mg/kg orally, suggesting that nepadutant reduced both intestinal motility and visceral sensitivity in animal models of IBS [14].

TALNETANT

This novel drug is a neurokinin3 receptor antagonist, which is being researched for several different functions, primarily for irritable bowel syndrome and as a potential antipsychotic drug for the treatment of schizophrenia [15].Talnetant and osanetant, are two structurally diverse antagonists of neurokinin-3 receptor (NK_3), which have definite roles in Ca^{2+} mobilization. Calcium and Magnesium play critical and antagonistic roles in regulating muscle function. Together they provide the mechanism for muscle contraction and relaxation.

Calcium has a constipating effect on the GI tract, whereas magnesium acts as a laxative [16].Studies have revealed that calcium supplements have beneficial roles for people with diarrhea-predominant IBS, and magnesium supplements in constipation predominant IBS.

PROBIOTICS

Are microorganisms which, when taken in adequate amounts, provide health benefits. Lactic acid bacteria and bifidobacteria are the most common types of microbes used as probiotic supplements. Probiotics are also naturally present in fermented foods. They improve intestinal microbial balance by inhibiting pathogens and toxin producing bacteria, thereby help normalize and maintain healthy gastrointestinal flora, which can minimize diarrhea, bloating, gas, and painful abdominal cramps. They are most effective when they are taken in conjunction with a prebiotic, which is an agent that encourages the growth of probiotics. Soluble fibers often have a prebiotic effect,

as their normal fermentation in the gut causes the production of beneficial short-chain fatty acids, which then lead to the growth of good gut flora. This in turn leads to a reduction (sometimes dramatic) in abdominal bloating and gas.

Probiotics are particularly effective when the gut is under assault from antibiotics therapy, though they can also be helpful when taken for daily maintenance. Quite a few research studies have shown that specific strains of probiotics can dramatically improve Irritable Bowel Syndrome symptoms [17]. Probiotic supplements should always be taken with food.

RIFAXIMIN

A semisynthetic antibiotic has additional advantages of low systemic absorption (more than 99 percent is secreted in the stool), good antibacterial activity, low microbial resistance and a high safety profile. Gut bacteria may be an underlying cause of IBS, and altering gut bacteria by treatment with rifaximin appears to be an effective way of providing relief to those who suffer from IBS symptoms. During the first four weeks after treatment, 40.7 percent of the patients in the rifaximin group reported adequate relief of global IBS symptoms, compared to 31.7 percent in the placebo group. Similarly, 40.2 percent in the rifaximin group had adequate relief of bloating, compared to 30.3 percent on placebo [18].In addition, significantly more patients taking the study drug reported adequate reductions of abdominal pain and loose or watery stools. Rifaximin at a dose of 550 milligram three times a day for 14 days provides better relief of IBS symptoms as compared to a placebo.

DEXLOXIGLUMIDE

Enteroendocrine cells in the duodenum and jejunum release cholecystokinin (CCK), which acts on vagal mucosal afferents leading to modulation of the gastric transit time and gastrocolonic response. Certain studies have shown that infusion of CCK in IBS patients induces pain and increased colonic response, [19]. suggesting a pronociceptive effect of CCK.

Dexloxiglumide, a cholecystokinin antagonist, selective for the CCK_A subtype thus inhibits the gastrointestinal motility and gastric secretions. So it is being investigated as a potential treatment for a variety of gastrointestinal problems like irritable bowel syndrome, [20] dyspepsia, [21] constipation [22]and pancreatitis [23]. A more recent study has reported that dexloxiglumide accelerates gastric emptying and delays ascending colonic transit with no effect on symptoms or bowel action in females with constipation-predominant IBS. Loxiglumide, another CCK-A receptor antagonist, reduced the pain perception of IBS symptoms in a study. However these agents are yet to be assessed fully for the potential treatment of visceral hypersensitivity.

MITEMCINAL

Motilin is an endogenous peptide hormone of 22 amino acids which stimulates gastric emptying in response to gastric distension or sham feeding and is involved in the induction of the migrating motor complex during the interdigestive period [24]. Mitemcinal is 3'-N-dimethyl-11-deoxy-3'-N-isopropyl-12-O-methyl-11-oxo-8,9-didehydroerythromycin,a motilin agonist derived from the macrolide antibiotic, erythromycin and has strong prokinetic effect but lacks the antibiotic properties of erythromycin. Prokinetics relieve symptoms of reflux by increasing the peristalsis thus speeds the clearance of food and acid from the oesophagus and stomach [25]. The effects of mitemcinal on defecation in experimental animals revealed that in normal dogs, orally administered mitemcinal increased stool weight in a dose-dependent manner without causing loose stools. At its highest tolerated dose, stool weight recovered was 83.9% as compared with that of untreated animals [26]. These results indicate that mitemcinal facilitates defecation without inducing severe diarrhea suggesting that mitemcinal may be a novel therapeutic agent for constipation for it enables easier control of defecation because of the early onset and short duration of its action.

DEXTOFISOPAM

Considering the role of the gut-brain axis, immune, neural, and endocrine pathways in the pathogenesis of IBS the possible beneficial effects of benzodiazepines (BZD) in this axis could be postulated.

BZD receptor modulators, reduce the visceral sensitivity and perception of pain. In a phase IIb Clinical trial of dextofisopam in 140 IBS patients, for 12 wk, the incidence of symptom relief was seen in 57% of patients as compared with a placebo .Although dextofisopam improved stool consistency in men and women, the recurrence rate was decreased only in females. The most common side effects were headache and abdominal pain (in 12% of patients in comparison with 4% in the placebo group) which was comparable to placebo [27].

DDP225 and DDP733

DDP225 for diarrhea-predominant irritable bowel syndrome (IBS-D) and DDP733 for constipation-predominant IBS (IBS-C). DDP225 is an oral low-potency inhibitor of both the $5\text{-}HT_3$ receptor and the

noradrenaline reuptake inhibitor. In a recently completed randomized, double-blind, placebo-controlled Phase IIa clinical trial, DDP225 demonstrated a statistically significant difference in the endpoint of adequate relief of IBS pain and discomfort as compared to a placebo. The drug was safe and well-tolerated in this study [28].

CONCLUSION

IBS is a commonly occurring syndrome, which is characterized by abdominal discomfort and bloating along with altered bowel habits. Its impact on patients can be quite severe, leading to great disruption in day-to-day activities. Researchers are not yet quite clear why people develop IBS. Often the disorder manifests itself following a severe bout of gastroenteritis, otherwise known as the stomach flu. Sometimes symptoms appear after the experience of an extremely stressful event. Some studies reveal a high incidence of IBS in adults who were the victim of sexual or physical abuse in childhood. Thus, stress and IBS often go hand in hand, but the relationship is not yet fully understood. New research avenues are looking at dysfunction in the neurochemical systems of the gut and the brain to understand better the role that stress plays in the onset and maintenance of IBS symptoms.

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